

What is claimed is:

sub
a1
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1. A synthetic oligonucleotide complementary to a portion of the HBV RNA and having a nucleotide sequence selected from the group consisting of SEQ ID NOS:1-31 and 42-48.

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2. The synthetic oligonucleotide of claim 1 having SEQ ID NO:1.

3. The synthetic oligonucleotide of claim 1 having SEQ ID NO:2.

15

4. The synthetic oligonucleotide of claim 1 having SEQ ID NO:3.

5. The synthetic oligonucleotide of claim 1 having SEQ ID NO:4.

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6. The synthetic oligonucleotide of claim 1 having SEQ ID NO:5.

7. The synthetic oligonucleotide of claim 1 having SEQ ID NO:6.

25

8. The synthetic oligonucleotide of claim 1 having SEQ ID NO:7.

SUB E3

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9. The synthetic oligonucleotide of claim 1 having SEQ ID NO:8.

10. The synthetic oligonucleotide of claim 1 having SEQ ID NO:9.

11. The synthetic oligonucleotide of claim 1
having SEQ ID NO:10.

12. The synthetic oligonucleotide of claim 1
having SEQ ID NO:11.

13. The synthetic oligonucleotide of claim 1
having SEQ ID NO:12.

14. The synthetic oligonucleotide of claim 1
having SEQ ID NO:13.

15. The synthetic oligonucleotide of claim 1
having SEQ ID NO:14.

16. The synthetic oligonucleotide of claim 1
having SEQ ID NO:15.

17. The synthetic oligonucleotide of claim 1
having SEQ ID NO:16.

18. The synthetic oligonucleotide of claim 1
having SEQ ID NO:17.

19. The synthetic oligonucleotide of claim 1
having SEQ ID NO:18.

20. The synthetic oligonucleotide of claim 1
having SEQ ID NO:19.

21. The synthetic oligonucleotide of claim 1
having SEQ ID NO:20.

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SUB E3

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SUB E3

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a3

SUB E3

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22. The synthetic oligonucleotide of claim 1
having SEQ ID NO:21.

5 23. The synthetic oligonucleotide of claim 1
having SEQ ID NO:22.

24. The synthetic oligonucleotide of claim 1
having SEQ ID NO:23.

10 25. The synthetic oligonucleotide of claim 1
having SEQ ID NO:24.

26. The synthetic oligonucleotide of claim 1
having SEQ ID NO:25.

15 27. The synthetic oligonucleotide of claim 1
having SEQ ID NO:26.

20 28. The synthetic oligonucleotide of claim 1
having SEQ ID NO:27.

29. The synthetic oligonucleotide of claim 1
having SEQ ID NO:28.

25 30. The synthetic oligonucleotide of claim 1
having SEQ ID NO:29.

31. The synthetic oligonucleotide of claim 1
having SEQ ID NO:30.

30 32. The synthetic oligonucleotide of claim 1
having SEQ ID NO:31.

33. The synthetic oligonucleotide of claim 1 having SEQ ID NO:42.

5 34. The synthetic oligonucleotide of claim 1 having SEQ ID NO:43.

35. The synthetic oligonucleotide of claim 1 having SEQ ID NO:44.

10 SUB E4 } 36. The synthetic oligonucleotide of claim 1 having SEQ ID NO:45.

15 37. The synthetic oligonucleotide of claim 1 having SEQ ID NO:46.

38. The synthetic oligonucleotide of claim 1 having SEQ ID NO:47.

20 39. The synthetic oligonucleotide of claim 1 having SEQ ID NO:48.

40. The synthetic oligonucleotide of claim 1 which is modified.

25 41. The oligonucleotide of claim 40 wherein the modification comprises at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorothioate, phosphorodithioate, alkylphosphonothioate, 30 phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, carboxymethyl ester, and combinations thereof.

42. The oligonucleotide of claim 41 comprising at least one phosphorothioate internucleotide linkage.

5 43. The oligonucleotide of claim 42 comprising phosphorothioate internucleotide linkages.

44. The oligonucleotide of claim 1 which comprises at least one deoxyribonucleotide.

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45. The oligonucleotide of claim 1 which comprises at least one ribonucleotide.

15 46. The oligonucleotide of claim 44 which comprises at least one ribonucleotide.

SUB FH 47. The oligonucleotide of claim 45 comprising at least one 2'-O-methyl nucleotide.

20 48. A kit comprising at least one oligonucleotide of claim 1.

49. A kit comprising at least two oligonucleotides of claim 1.

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SUB ES 50. A pharmaceutical composition comprising at least one oligonucleotide of claim 1.

30 51. A pharmaceutical composition comprising at least two different oligonucleotides of claim 1.

52. A method of inhibiting HBV replication in a cell, comprising the step of administering to the cell a therapeutic amount of a pharmaceutical composition comprising at least one synthetic oligonucleotide,

the synthetic oligonucleotide being complementary to a portion of HBV RNA and having a sequence selected from the group consisting of SEQ ID NOS:1-31 and 42-48.

53. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:1.

54. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:2.

55. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:3.

56. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:4.

57. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:5.

58. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:6.

59. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:7.

60. The method of claim 52 wherein the oligonucleotide administered has SEQ ID NO:8.

61. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:9.

5 62. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:10.

63. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:11.

10 64. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:12.

65. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:13.

15 66. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:14.

20 67. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:15.

68. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:16.

25 69. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:17.

70. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:18.

30 71. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:19.

72. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:20.

5 73. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:21.

74. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:22.

10 75. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:23.

76. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:24.

15 77. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:25.

20 78. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:26.

79. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:27.

25 80. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:28.

81. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:29.

30 82. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:30.

83. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:31.

5 84. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:42.

85. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:43.

10 86. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:44.

15 87. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:45.

88. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:46.

20 89. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:47.

90. The method of claim 52 wherein the
oligonucleotide administered has SEQ ID NO:48.

25 91. The method of claim 52 wherein at least two
different oligonucleotides are administered.

92. A method of treating HBV infection,
comprising the step of administering to an
infected animal or cell a therapeutic amount of a
pharmaceutical composition comprising at least one
5 synthetic oligonucleotide,

the synthetic oligonucleotide being
complementary to a portion of HBV RNA and having a
sequence selected from the group consisting of SEQ
ID NOS:1-31 and 42-48.

10 93. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:1.

15 94. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:2.

95. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:3.

20 96. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:4.

97. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:5.

25 98. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:6.

30 99. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:7.

100. The method of claim 92 wherein the synthetic
oligonucleotide administered has SEQ ID NO:8.

101. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:9.

5 102. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:10.

103. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:11.

10 104. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:12.

105. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:13.

15 106. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:14.

20 107. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:15.

108. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:16.

25 109. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:17.

30 110. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:18.

111. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:19.

112. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:20.

5 113. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:21.

114. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:22.

10 115. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:23.

116. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:24.

15 117. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:25.

20 118. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:26.

119. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:27.

25 120. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:28.

30 121. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:29.

122. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:30.

123. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:31.

5 124. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:42.

125. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:43.

10 126. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:44.

15 127. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:45.

128. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:46.

20 129. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:47.

130. The method of claim 92 wherein the synthetic oligonucleotide administered has SEQ ID NO:48.

25 131. The method of claim 92 wherein at least two different synthetic oligonucleotides are administered to the animal or cell.

30 132. A synthetic oligonucleotide complementary to at least two noncontiguous regions of an HBV nucleic acid.

133. The synthetic oligonucleotide of claim 132 complementary to at least two noncontiguous regions in the epsilon region of the precore gene.

5 134. The oligonucleotide of claim 132 having about 20 to about 30 nucleotides.

135. The synthetic oligonucleotide of claim 132 which is modified.

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136. The oligonucleotide of claim 135 wherein the modification comprises at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorothioate, phosphorodithioate, alkylphosphonothioate, 15 phosphoramidate, carbamate, carbonate, phosphate triester, acetamdate, carboxymethyl ester, and combinations thereof.

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137. The oligonucleotide of claim 136 comprising at least one phosphorothioate internucleotide linkage.

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138. The oligonucleotide of claim 137 having phosphorothioate internucleotide linkages.

139. The oligonucleotide of claim 137 comprising at least one 2'-O-methyl.

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140. The oligonucleotide of claim 132 comprising at least one deoxyribonucleotide.

141. The oligonucleotide of claim 140 comprising at least one ribonucleotide.

142. The oligonucleotide of claim 140 comprising at least one ribonucleotide.

5 143. The oligonucleotide of claim 141 comprising at least one 2'-O-methyl.

10 144. The oligonucleotide of claim 132 comprising a sequence selected from the group consisting of SEQ ID NOS:32-41.

145. The synthetic oligonucleotide of claim 144 having SEQ ID NO:32.

15 146. The synthetic oligonucleotide of claim 144 having SEQ ID NO:33.

147. The synthetic oligonucleotide of claim 144 having SEQ ID NO:34.

20 148. The synthetic oligonucleotide of claim 144 having SEQ ID NO:35.

149. The synthetic oligonucleotide of claim 144 having SEQ ID NO:36.

25 150. The synthetic oligonucleotide of claim 144 having SEQ ID NO:37.

30 151. The synthetic oligonucleotide of claim 144 having SEQ ID NO:38.

152. The synthetic oligonucleotide of claim 144 having SEQ ID NO:39.

153. The synthetic oligonucleotide of claim 144 having SEQ ID NO:40.

5 154. The synthetic oligonucleotide of claim 144 having SEQ ID NO:41.

155. A pharmaceutical composition comprising at least one oligonucleotide of claim 132.

10 156. The pharmaceutical composition comprising at least two different oligonucleotides of claim 132.

15 157. A kit for inhibiting HBV replication and/or infection in a cell comprising at least one synthetic oligonucleotide of claim 132.

20 158. A kit for inhibiting HBV replication and infection in a cell comprising at least two synthetic oligonucleotides of claim 132.

25 159. A method of inhibiting HBV replication in a cell comprising the step of administering to the cell a therapeutic amount of a pharmaceutical composition comprising at least one synthetic oligonucleotide,

the synthetic oligonucleotide being complementary to at least two noncontiguous regions of HBV RNA.

30 160. The method of claim 159 wherein at least two different oligonucleotides are administered.

161. The method of claim 159 wherein the synthetic oligonucleotide administered is complementary to at least two noncontiguous regions in the epsilon region of the precore gene.

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162. The method of claim 159 wherein the oligonucleotide administered has about 20 to about 30 nucleotides.

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163. The method of claim 159 wherein the oligonucleotide administered is modified.

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164. The method of claim 163 wherein the oligonucleotide administered comprises at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorothioate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, carboxymethyl ester, and combinations thereof.

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165. The method of claim 164 wherein the oligonucleotide administered comprises at least one phosphorothioate internucleotide linkage.

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166. The method of claim 165 wherein the oligonucleotide administered has phosphorothioate internucleotide linkages.

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167. The method of claim 165 wherein the oligonucleotide administered further comprises at least one 2'-O-methyl nucleotide.

168. The method of claim 159 wherein the oligonucleotide administered comprises at least one deoxyribonucleotide.

5 169. The method of claim 159 wherein the oligonucleotide administered comprises at least one ribonucleotide.

10 170. The method of claim 168 wherein the oligonucleotide administered further comprises a least one ribonucleotide.

15 171. The method of claim 169 wherein the oligonucleotide administered further comprises at least one 2'-O-methyl nucleotide.

20 172. The method of claim 159 wherein the synthetic oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NOS:32-41.

173. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:32.

25 174. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:33.

175. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:34.

30 176. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:35.

177. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:36.

178. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:37.

5 179. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:38.

180. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:39.

10 181. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:40.

15 182. The method of claim 172 wherein the synthetic oligonucleotide comprises SEQ ID NO:41.

183. A method of treating HBV infection comprising the step of administering to an infected animal or cell a therapeutic amount of a pharmaceutical composition comprising at least one synthetic oligonucleotide,

20 the synthetic oligonucleotide being complementary to at least two noncontiguous regions of HBV RNA.

25 184. The method of claim 183 wherein at least two different oligonucleotides are administered.

30 185. The method of claim 183 wherein the synthetic oligonucleotide administered is complementary to at least two noncontiguous regions in the epsilon region of the precore gene.

186. The method of claim 183 wherein the oligonucleotide administered has about 20 to about 30 nucleotides.

5 187. The method of claim 183 wherein the oligonucleotide administered is modified.

188. The method of claim 187 wherein the oligonucleotide administered comprises at least
10 one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorothioate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate,
15 carboxymethyl ester, and combinations thereof.

189. The method of claim 188 wherein the oligonucleotide administered comprises at least
20 one phosphorothioate internucleotide linkage.

190. The method of claim 189 wherein the oligonucleotide administered has phosphorothioate internucleotide linkages.

25 191. The method of claim 189 wherein the oligonucleotide administered further comprises at least one 2'-O-methyl nucleotide.

192. The method of claim 183 wherein the
30 oligonucleotide administered comprises at least one deoxyribonucleotide.

193. The method of claim 183 wherein the oligonucleotide administered comprises at least one ribonucleotide.

5 194. The method of claim 192 wherein the oligonucleotide administered further comprises a least one ribonucleotide.

10 195. The method of claim 193 wherein the oligonucleotide administered further comprises at least one 2'-O-methyl nucleotide.

15 196. The method of claim 183 wherein the synthetic oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NOS:32-41.

197. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:32.

20 198. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:33.

25 199. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:34.

200. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:35.

30 201. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:36.

202. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:37.

203. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:38.

5 204. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:39.

205. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:40.

10 206. The method of claim 196 wherein the synthetic oligonucleotide comprises SEQ ID NO:41.

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